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(54) **Coated biomaterials and methods for making same**

Beschichtete Biomaterialien und Verfahren zu ihrer Herstellung

Biomatériaux revêtus et leur procédé de fabrication

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(56) References cited:

EP-A- 0 022 724	EP-A- 0 159 087
EP-A- 0 230 570	EP-A- 0 278 583
WO-A-86/01726	FR-A- 2 223 325

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EP 0 395 187 B1

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Description

BACKGROUND OF THE INVENTION

This invention relates to biomaterials useful in bone repair and replacement, especially as used for orthopedic, dental and oral surgery. More particularly, this invention relates to biomaterials having a special surface which resorbs more slowly than the underlying base.

Porous carbonate echinoderm or scleractinian skeletal material of marine life has a unique structure. This material has a uniformly permeable interconnected three dimensional porosity characterized by a substantially uniform pore volume in the range from 10 to 90%. The microstructure of this material resembles the cancellous structure characteristic of bony tissue or bone. Because of this unique microstructure of the porous carbonate echinoderm or scleractinian coral skeletal material of marine life, these materials are useful as bone substitutes. However, the carbonates of this material, such as provided in echinoid spine calcite and Porites skeletal aragonite, do not have the desired durability for use as bone substitutes.

A technique has been developed to convert the foregoing calcium carbonate coral materials to hydroxyapatite while at the same time retaining the unique microstructure of the coral material. U.S. Patent No. 3,929,971 (incorporated herein by reference) discloses a hydrothermal exchange reaction for converting the porous carbonate skeletal material of marine life into a phosphate or hydroxyapatite skeletal material possessing the same microstructure as the carbonate skeletal material. These synthetic hydroxyapatite materials have been produced commercially and are available from Interpore International Inc., Irvine, California, under the tradename Interpore-200, which is derived from certain coral of the genus Porites, which have an average pore diameter of about 200 microns, and under the tradename Interpore-500 derived from certain members of the family Goniopora, which have pore diameters of about 500 microns.

Interpore-200 and Interpore-500, have also been identified as replamineform hydroxyapatite and coralline hydroxyapatite, have been found to be useful as bone substitute materials in dental and surgical applications. These materials are essentially nondegradable. More information concerning these materials can be found in the article by Eugene White and Edwin C. Shors entitled "Biomaterial Aspects of Interpore-200 Porous Hydroxyapatite", which appeared in Dental Clinics of North America, Vol. 30, No. 1, January 1986, pp. 49-67, incorporated herein by reference.

However, while calcium phosphates such as Interpore-200 and Interpore-500 are satisfactory for many applications, and promote the ingrowth of bone and other tissue into and around the implant, they do not satisfy all of the needs of surgeons using them as bone replacements or implants.

For some applications, surgeons prefer that bone substitutes resorb within a few weeks or months following implantation, after new bone has grown through the implant site. One approach to increase the degradation rate of ceramic implants has been to use tricalcium phosphate instead of hydroxyapatite. Tricalcium phosphate degrades, but its rate of degradation is inconsistent and unpredictable. Another approach utilizes polymers that are biodegradable and non-toxic to the host into whom the polymer is implanted. However, there is little evidence that these materials are osteoconductive or have adequate interconnected porosity.

Accordingly, it is an object of this invention to provide a ceramic biomaterial which degrades in a predictable manner and at an acceptable rate.

It is another object of this invention to provide bone substitute materials and methods for their manufacture derived from solid or porous calcium carbonate and having a surface layer of hydroxyapatite.

It is a further object of this invention to provide bone substitute materials derived from coral having the unique porous microstructure thereof, while having a more slowly resorbing layer of calcium phosphate or hydroxyapatite.

It is a still further object of the invention to provide bone substitute materials which include a calcium phosphate layer throughout the porous structure of coral without compromising the porosity of the structure or its interconnectedness.

It is another object of the invention to provide solid or porous calcium carbonate granules having calcium phosphate surface regions.

It is a further object of the invention to provide a degradable biomaterial which provides an adherent surface for growth factors and antibiotics.

How these and other objects of this invention are achieved will become apparent in light of the accompanying disclosure.

SUMMARY OF THE INVENTION

The present invention is directed to an improved biomaterial which can support bone ingrowth but which will degrade at a controlled rate, allowing bone to fill the voids left by the degrading implant.

According to the invention, a biomaterial is provided which has a base portion of calcium carbonate and a surface layer of calcium phosphate or hydroxyapatite. The calcium carbonate is porous throughout and is derived from coral skeletal material. The calcium carbonate at the surface of a coral skeletal sample is converted to calcium phosphate

preferably by a hydrothermal chemical exchange reaction with a phosphate such as ammonium phosphate. The phosphate or hydroxyapatite surfaced calcium carbonate biomaterial may be used to replace portions of the bony animal skeletal structure, such as bone implants and prostheses and dental implants and prostheses, or any application where a resorbable implant seems advantageous.

Alternatively, the present invention can be practiced by providing granules of the phosphate or hydroxyapatite surfaced calcium carbonate biomaterial having diameters of 400 microns to 5 mm. The granules may be derived from porous coral or other marine life or may be essentially non-porous granules whose surface is converted to phosphate or hydroxyapatite by a hydrothermal conversion process.

In some applications, the pores of the phosphate or hydroxyapatite surfaced calcium carbonate biomaterial derived from skeletal marine life such as coral can be filled with a biocompatible polymer. The polymer may itself be degradable by the host into which it is implanted or it may be nondegradable, depending on the proposed use. Degradable polymers preferably include polyglycolic acid or polylactic acid, while nondegradable polymers may include polysulfones, silicone rubber, polyurethane, ultrahigh molecular weight polyethylene, or other polymers known to be nontoxic and implantable in humans. In some uses, it may be advantageous after filling the pores with the polymer to remove the phosphate or hydroxyapatite layer on the outer surface of the biomaterial to expose the calcium carbonate and dissolve away some or all of the calcium carbonate to form a porous hydroxyapatite and polymer biomaterial.

Preferably, the biomaterials of the present invention are made by converting the surface of a calcium carbonate sample to calcium phosphate, in the crystalline form hydroxyapatite. The conversion is accomplished by a hydrothermal chemical exchange with a phosphate, such as ammonium phosphate, and the thickness of the phosphate layer on the surface of the calcium carbonate may be controlled by varying the concentration of the phosphate employed in the process.

The invention, together with further objects and attendant advantages, will be best understood by reference to the following detailed description taken in conjunction with the accompanying drawing.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is a rendering of an actual photomicrograph (magnified 150x) of a section of biomaterial of this invention showing the calcium carbonate base portion and calcium phosphate or hydroxyapatite surface layer; and

FIGURE 2 is a rendering of an actual photomicrograph (160x) showing a cross-section of an implant made from the biomaterial of this invention that had been implanted several months earlier in an animal.

DESCRIPTION OF THE PREFERRED EMBODIMENT

Hydroxyapatite is widely used as a bone substitute material in oral, periodontal and craniofacial surgery, and is under investigation for various orthopedic applications, such as bone replacements due to trauma, spinal fusions, tumors, joint surgery and the like. The biocompatibility of hydroxyapatite is well established and it is available commercially, mostly for oral surgery applications, in dense and porous forms. Hydroxyapatite promotes bone ingrowth in and around the implant, but even the porous form is resorbable only at a rate of 1-2 percent annually. Dense hydroxyapatite is essentially nonresorbable over a period of years.

In accordance with the present invention, the surface carbonate making up the microstructure of porous permeable animal carbonate skeletal material, such as the porous, permeable carbonate skeletal material of marine life, e.g. the porous skeletal material of marine invertebrates, such as echinoid spine calcite, Porites skeletal aragonite and Goniopora skeletal aragonite (both calcite and aragonite being carbonates) has been converted into whitlockite and hydroxyapatite by hydrothermal chemical exchange with a phosphate. The resulting produced synthetic phosphate (hydroxyapatite or whitlockite) surfaced skeletal material possesses substantially the same microstructure of the original carbonate skeletal material from which it was derived. These synthetic materials are useful for the manufacture of prosthetic devices, such as body and bone implants, tooth fixation, massive hard tissue replacements and the like since hydroxyapatite and whitlockite are biocompatible materials.

The thin layer of hydroxyapatite resorbs slowly after allowing bone and other tissue to grow into the pores during an initial repair period during which the surrounding bone can form a repair network. After the hydroxyapatite resorbs enough to expose the underlying base of calcium carbonate, the degradation process speeds up owing to the more rapid degradation of calcium carbonate as compared with hydroxyapatite. This allows even more bone ingrowth to occur, eventually permitting complete replacement of the artificial part with new bone and other tissue.

Whitlockite seems to degrade more rapidly than hydroxyapatite, and whitlockite surfaced calcite structures may be used where more rapid initial degradation is desired. However, it is preferred that the rate of degradation be modulated or controlled by varying the thickness of the hydroxyapatite coating which can be conveniently accomplished by varying the concentration of the phosphate solution used in the conversion process.

The synthetic phosphate materials prepared in accordance with this invention, as indicated hereinabove, are particularly useful as biomaterials for use in the manufacture of prosthetic devices or for use as implants in human hard tissue and the like. The surface of the materials of this invention, particularly those made from porous carbonate (aragonite) skeletal material of marine life, since they are comprised predominantly of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ with some carbonate (CO_3) present, approximate the composition of the inorganic component of human hard tissue, i.e., human bone. This hydroxyapatite surface has osteophilic and osteoconductive properties, and helps promote the growth of bone tissue into the porosity of the biomaterial.

Materials of this invention would preferably have a microstructure which is porous, completely interconnected, approximating the same pore size as cancellous human bone which would allow permeation of body fluids and blood cells thereinto. Materials in accordance with this invention could be prepared which would be suitable for root portions of tooth implants and mandibular restorations where it would permit rapid ingrowth of periodontal and hard tissue, as well as other bone repair functions such as segmental bone replacements for bone fractures, tumors, joint surgery and spinal fusion.

As indicated, various porous carbonate skeletal materials, particularly porous carbonate skeletal material of marine life, may be employed in the practices of this invention. Particularly useful, because of the vast quantities available, is the carbonate skeletal material of scleractinian coral Porites wherein the skeletal material is composed of the carbonate aragonite, and the average pore size is approximately 200 microns. Other corals of the genera Goniopora, Alveopora, Acropora and others may be suitable employed in the practice of this invention as the source of the carbonate skeletal material for conversion by hydrothermal chemical exchange with a phosphate into hydroxyapatite. Goniopora has an average pore size of about 500 microns, and includes pores ranging in size from 5 microns to 1000 microns.

Where the carbonate skeletal material is made up of a calcite carbonate marine skeletal material, such as echinoid spine calcite where the calcite contains a substantial amount of magnesium associated therewith, whitlockite is produced upon hydrothermal chemical exchange with a phosphate on the surface of the biomaterial. Both materials, however, hydroxyapatite and whitlockite, are useful materials, with the hydroxyapatite being preferred for the manufacture of a prosthetic device and the like.

Alternatively, the biomaterials of the present invention can be made in the form of porous or non-porous granules having a surface layer of hydroxyapatite (or whitlockite) on a base of porous or solid calcium carbonate. These granules can be dispensed into a cavity where bone repair is desired using a syringe adapted to deliver the particles into the cavity. The irregular surfaces of the particles create spaces between adjacent ones, permitting bone and other tissue to grow around the particles, and in the case of porous particles, into their pores. The particles of the present invention are particularly useful for dental application such as reconstruction of the aveolar ridge and for filling periodontal spaces. For periodontal use, granules having an average nominal diameter of about 425-600 microns and an average pore size of about 200 microns should be used; for reconstruction of the aveolar ridge, granules having an average nominal diameter of 425 to 1000 microns and an average pore size of about 200 microns can be used. For orthopedic applications, larger granules having an average nominal diameter of 1-2 mm or 3-5 mm can be used.

In the manufacture of the synthetic materials of this invention it would be desirable, before subjecting the naturally occurring porous carbonate skeletal material to hydrothermal chemical exchange with a phosphate, to first prepare the porous carbonate skeletal material by the removal of any organic material therefrom. A suitable technique for the removal of organic material from the porous skeletal material would be by immersion in a dilute (about 5%) aqueous solution of sodium hypochlorite. Usually an immersion time of about 30 hours is satisfactory for the removal of substantially all of the organic matter. Following this the material is rinsed, preferably in deionized water, and dried, such as at a temperature of about 90°C. Any suitable technique for the removal of organic material, such as the technique for the removal of organic matter from animal bone described in SCIENCE, 119, 771 (1954), might be employed. If desired, the organic-free carbonate skeletal material after conversion by hydrothermal chemical exchange with a phosphate to hydroxyapatite or whitlockite, if not already shaped, may be shaped into a desired form or structure, for example, cylinders, screws, nuts, bolts, pins, flat or curved plates and the like.

The conversion of porous carbonate skeletal materials into the phosphate surfaced carbonate biomaterials of the present invention preferably involves lower temperature and pressures than those disclosed in U.S. Patent No. 3,929,971. The conversion may be carried out by placing blocks or granules of calcium carbonate in phosphate solution or by freeze drying the phosphate onto the carbonate base and then carrying out the hydroconversion in a steam filled autoclave preferably at a temperature from 180°C to 330°C, for a period of time of 1 hour to 2 weeks, preferably 10 to 72 hours. Preferred temperatures range from 200-250°C, with about 200-230°C appearing optimum. Preferably, the pressure should be that developed in a sealed vessel or autoclave by the steam contained therein, which is estimated to be $3.55 \cdot 10^3$ to $27.7 \cdot 10^3$ kPa (500 to 4000 p.s.i.). If the conversion is carried out in a phosphate solution, such as ammonium phosphate, the temperature should preferably be about 230°C and the pressure should be preferably about $7.0 \cdot 10^3$ kPa (1000 p.s.i.), and the reaction should be carried out for 10 to 60 hours.

The chemical reaction involved in the conversion of calcium carbonate to hydroxyapatite is as follows:

$$10\,CaCO_3 + 6(NH_4)_2HPO_4 + 2HO_2\ Ca_{10}\,(PO_4)_6(OH)_2 + 6\,(NH_4)_2CO_3 + 4H_2CO_3$$

Various substantially water-soluble phosphates may be employed as the phosphate contributing reactant in the hydrothermal chemical exchange reaction to produce the special materials of this invention. The preferred phosphates include ammonium phosphates and orthophosphates. Also useful would be the calcium orthophosphates and the acid phosphates, as well as orthophosphoric acid including its hydrates and derivatives and mixtures of a weak acid, such as acetic acid, with a phosphate.

Other orthophosphates and acid phosphates useful in the practices of this invention include $Li_3(PO_4)$, $LiH_2(PO_4)$, $Na_3(PO_4)$, Na_2HPO_4, $Na_3H_3(PO_4)_2$, $NaH_2(PO_4)$, $Na_4H_5(PO_4)_3$, $NaH_5(PO_4)_2$, K_3PO_4, K_2HPO_4, $K_7H_5(PO_4)_4$, $K_5H_4(PO_4)_3$, $KH_2(PO_4)$, $KH_5(PO_4)_2$, $(HN_4)_3PO_4$, $(NH_4)_2HPO_4$, $NH_4H_2PO_4$, $NH_4H_5(PO_4)_2$, $NH_4H_8(PO_4)_3$, and their hydrates, and mixed salts especially of K, NH_4 and Na orthophosphates and acid phosphates, including also Rb and Cs orthophosphates and acid phosphates. Also useful in addition to the aforementioned are the calcium orthophosphates $2CaO.P_2O_5$, $CaHPO_4$, $Ca_4P_2O_9$, $Ca(H_2PO_4)_2$ and $CaO.P_2O_5$.

Upon completion of the hydrothermal chemical exchange reaction it has been shown by examination including optical microscopy and scanning electron microscopy, that the resulting three-dimensional completely interpenetrating porous structure is the same as the original carbonate structure from which it was derived. The original calcium carbonate (aragonite) crystal structure of the resulting produced material is absent as determined by x-ray diffraction and by optical microscopy.

The following is illustrative of the preferred methods of making the biomaterials of the present invention. A cylinder 2.22 cm (7/8 inch) diameter by 2.54 cm (one inch) was machined from a head of Porites coral. The Porites coral cylinder was cleaned ultrasonically to remove machining debris then rinsed and dried. The dried cylinder weighed 16.7gm and fit into the Teflon liner of a test size reaction vessel. To the dry Teflon liner (87.0gm) was added 7.6gm distilled H_2O and 5.6gm $(NH_4)_2HPO_4$. The Teflon liner and contents were preheated in 80°C oven and contents stirred to dissolve phosphate. The coral cylinder prepared above was lowered into the 80°C solution, the Teflon liner with contents was placed in preheated stainless steel vessel and sealed. The sealed vessel was placed in a 220°C oven and held at 220°C for 12 hours. The vessel was allowed to cool down after which it was opened. After rinsing in distilled water and drying, the weight of hydroxyapatite-coated coral was 16.4gm. Stereoptic microscope examination revealed excellent pore fidelity and no cracks.

In another variation of the method, samples of coral, either Porites or Goniopora, are cut with dimensions varying from 8mm x 8mm x 3mm to 30mm x 70mm x 15mm rods or any other desired shape. The coral is cleaned by immersion in standard chlorine bleach (sodium hypochlorite) for 24 hours, then rinsed several times in water, and then completely dried. The blocks of coral are then weighed.

Solutions of ammonium dibasic phosphate ($(NH_4)_2HPO_4$) approximately 5-40 percent by weight (Baker Chemicals, Catalog #0784-05) are made by dissolving the salt in deionized water. The dry blocks of coral are individually weighed and placed in separate polyethylene bags with sealable tops. An ammonium phosphate solution is then piped into the bags to totally immerse the blocks. The bags are transferred to a vacuum chamber and the blocks are degassed to fully infiltrate the solution into the pores. The tops to the bags are then closed, making sure that the blocks remain fully submerged. The bags are then transferred to a conventional freezer (approximately 15°C) for approximately 24 hours to freeze the blocks. The frozen blocks and solution are then removed from the bags and placed in a freeze-drying chamber. Freeze-drying is performed in a vacuum (less than $13.3 \cdot 10^{-3}$ kPa (0.1 Torr)) at a temperature of 35°C for at least 24 hours. The excess dried ammonium phosphate crust around the blocks is then removed from the surface by scraping. The blocks are weighed and the percent weight gain is determined.

Carbonate to phosphate substitution by hydrothermal conversion is then performed using a 750ml high pressure autoclave (Berghof America, Catalog #7400) having a Teflon liner, filled with approximately 200ml of deionized water. A Teflon platform is placed on the bottom of the liner such that the upper surface is above the waterline. The blocks are then stacked on the platform with Teflon webbing acting as a spacer between successive layers of the blocks. Species of coral and concentrations of ammonium phosphate can be mixed without cross-contamination. The top to the conversion vessel is closed and the vessel is placed in a conventional convection oven (Blue M, Catalog #POM7-136F-3). The temperature is gradually raised to 230° and held there for about 60 hours. A pressure of about $7.0 \cdot 10^3$ kPa (1000 psi) is generated by the vapor pressure of steam and the reactants at the stated temperature. At completion of the hydrothermal conversion, the reaction vessel is opened and blocks removed. The thickness of the coating has been observed to be directly proportional to the concentration of ammonium phosphate solution used at the immersion step and to the weight gain for each of the two species of coral. The Goniopora coral results in a thicker coating than the Porites coral for the same concentration of ammonium phosphate, because the Goniopora has a larger void fraction and a smaller specific surface area.

The thickness of the hydroxyapatite-coating is dependent on the concentration of ammonium phosphate used with the freeze dried treatment. The thicknesses of the coating achieved experimentally on Porites coral are:

% HA Solution	Thickness of Coating (µm)	Range (µm)
5%	0.8	0.6-1.2
10%	2.0	1.2-2.5
20%	3.4	3.1-3.8
30%	4.7	3.7-5.6
40%	6.19	6.2-7.5

The thickness on the Goniopora coral is a follows:

% Ammonium Phosphate	Thickness of Coating	Range (µm)
5%	3.8	3.1-4.4
10%	5.6	5.0-6.3
20%	10.6	10.0-11.2
30%	13.7	12.5-15.0
40%	20.6	18.7-22.5

A biomaterial made in accordance with this process was embedded in a suitable medium (Spurr's Embedding Medium) and polished. FIG. 1 is an example of a photomicrograph from a scanning electron microscope with backscatter detector illustrating as sample of a porous biomaterial made from Porites coral. A distinct surface layer of phosphate 10 was present on all surfaces of the calcium carbonate 12, and appeared uniform throughout the structure. The thickness of the hydroxyapatite layer 10 was directly proportional to the concentration of the ammonium dibasic phosphate solution used to fabricate the biomaterial. The unique porous microstructure of the coral was preserved.

To determine the composition of a sample of the biomaterial, energy dispersive x-ray analysis was performed on the hydroxyapatite surface layer and the calcium carbonate core of a sample made with Goniopora coral and 30% ammonium dibasic phosphate solution. The results from the analysis of the hydroxyapatite surface layer or region are set forth in the accompanying Table 1, while the results from analysis of the calcium carbonate core are set forth in the accompanying Table 2. These tests demonstrated that the surface layer was rich in phosphate (about 47%), whereas

the center core of coral material had essentially no phosphate.

TABLE 1

Center Core Analysis

Accelerating voltage	20.0 KeV
Beam - sample incidence angle	70.0 degrees
Xray emergence angle	29.4 degrees
Xray - window incidence angle	9.1 degrees
Window thickness	12.0 microns

STANDARDLESS EDS ANALYSIS
(ZAF CORRECTIONS VIA MAGIC V)

ELEMENT & LINE	WEIGHT PERCENT	ATOMIC PERCENT*	PRECISION 3 SIGMA	K-RATIO**	ITER
P KA	0.36	0.46	0.11	0.0028	
Ca KA	99.84	99.54	0.51	0.9972	2
TOTAL	100.00				

*NOTE: ATOMIC PERCENT is normalized to 100

**NOTE: K-RATIO = K-RATIO x R
where R - reference(standard)/reference(sample)

NORMALIZATION FACTOR: 0.998

TABLE 2

Surface Analysis

Accelerating voltage	20.0 KeV
Beam - sample incidence angle	70.0 degrees
Xray emergence angle	29.4 degrees
Xray - window incidence angle	9.1 degrees
Window thickness	10.0 microns

STANDARDLESS SKS ANALYSIS
(ZAF CORRECTIONS VIA MAGIC V)

ELEMENT & LINE	WEIGHT PERCENT	ATOMIC PERCENT*	PRECISION 3 SIGMA	K-RATIO	ITER
P KA	34.96	41.02	0.38	0.3364	
Ca KA	65.04	58.98	0.49	0.6636	4
TOTAL	100.00				

*NOTE: ATOMIC PERCENT is normalized to 100

**NOTE: K-RATIO = K-RATIO x R
where R = reference(standard)/reference(sample)

NORMALIZATION FACTOR: 0.882

To make coatings on granules, granules of either solid calcium carbonate (Mallinkrodt Chemicals, Catalog 6210) or porous calcium carbonate derived from corals (<u>Porites</u>, 425-1000 μm in diameter and <u>Goniopora</u>, 0.5 mm in diameter) are placed in plastic bags as described above. The ammonium phosphate ($(NH4)_2HPO_4$) is added, frozen and freeze-dried. Hydrothermal conversion is accomplished by placing the freeze-dried granules in porous Teflon bags or in separate Teflon beakers, and then heating the sample in a closed container as discussed above.

Another embodiment of the present invention combines the osteophyllic and osteoconductive properties of hydroxyapatites with biocompatible polymers used as implants. A hydroxyapatite coated porous calcium carbonate composite is prepared as described above. The porosity of the composite is filled with polymer either with positive injection pressure or by vacuum impregnation. Examples of polymers suitable for the practice of this invention include polysulfone, polyethylene, such as ultrahigh molecular weight polyethylene, silicone rubber (Dow Corning) or polyurethane (Thermedics Inc., Tecoflex).

After solidification of the polymer, the composite may optionally be trimmed on all surfaces to expose the calcium carbonate structure. The composite is then immersed in 10% acetic acid. This preferentially dissolves the calcium carbonate leaving behind the hydroxyapatite and polymer. An interconnected porous structure remains that is lined with hydroxyapatite and has an infrastructure of the polymer. Alternatively, the calcium carbonate is not dissolved away, or only partially dissolved away. After implantation in the body, however, the body preferentially degrades the calcium carbonate leaving the hydroxyapatite coating which degrades more slowly, and the polymer.

In another embodiment, the porosity of the hydroxyapatite coated composite may be filled with a polymer which may be degraded by the body after implantation. Examples of such polymers include polylactic, polyglycolic acid or polycaprolactone (Union Carbide). With implants made in accordance with this embodiment, the calcium carbonate may be removed or left intact, depending upon the desired properties of the implant. The polymer in such an implant degrades after implantation, as does the calcium carbonate, when present. The dissolution of polymer and calcium carbonate provides additional space for bone or tissue ingrowth.

The biomaterials of the present invention provide several important and unique advantages. The hydroxyapatite surface layer degrades slowly as compared to calcium carbonate and helps modulate degradation. The implant will degrade only slowly at first, allowing the bone or other tissue to fill the interconnected porous network. Thus ingrowth can occur prior to resorbtion.

FIG. 2 illustrates an implant 18 of the biomaterial of the present invention made by hydroconversion of Goniopora with 5% ammonium phosphate, which was implanted for approximately 12 weeks in a rabbit tibia. The implant 18 includes the calcium carbonate base 20 and the hydroxyapatite or phosphate surface 22 surrounded by bone 24. As shown in FIG. 2, once cracks or fissures appear in the hydroxyapatite surface 22 exposing the underlying calcium carbonate 20, degradation accelerates since calcium carbonate appears to degrade more rapidly than does hydroxyapatite. Bone 24 can be seen replacing the space 20a formerly filled with calcium carbonate 20.

Another advantage of the hydroxyapatite layer in the biomaterial of the present invention is its inherent osteophilic nature. That is, hydroxyapatite on the surface of a porous implant seems to promote bone ingrowth into the pores of the implant, whereas calcium carbonate seems not to possess this property.

Another advantage of hydroxyapatite is absorbency, which may explain its ability to bind other compositions which aid in the bone repair process. An antibiotic such as tetracycline, oxytetracycline or other known synthetic or semisynthetic antibiotic may be introduced unto the pore cavities of the implant. Likewise, one of several growth factors such as transforming growth factor or one of the Bone Morphogenic Proteins can be attached which help promote bone ingrowth. For example, transforming growth factor β (TGF-β) is believed to have a role in transforming undifferentiated primitive mesenchymal cells observed at the leading edge of bone ingrowth into bone cells. TGF-β can be added to the hydroxyapatite surface after hydroconversion to help enhance bone ingrowth. Alternatively, growth factor or an antibiotic can be intermixed with a preferably biodegradable polymer and injected or vacuum infiltrated into the porosity of the phosphate surfaced carbonate biomaterial.

Claims

1. A biomaterial comprising a base portion comprising calcium carbonate consisting essentially of coral skeletal material and having a surface layer of synthetic phosphate converted from said calcium carbonate, in which surface layer the porous microstructure of said coral skeletal material is preserved.

2. A biomaterial as recited in Claim 1 having a three dimensional porous microstructure corresponding to the microstructure of porous carbonate echinoderm or schleractinian coral skeletal material.

3. A biomaterial as recited in Claim 1 wherein said surface layer has a thickness less than about 25 microns.

4. A biomaterial as recited in Claim 2 wherein said base portion is porous calcium carbonate derived from coral.

5. A biomaterial as recited in Claim 2 wherein said base portion is Goniopora or Alveolopora coral and said surface layer consists essentially of hydroxyapatite.

6. A biomaterial as recited in Claim 2 having pore sizes in the range of 5-1000 microns, preferably having substantially uniform pore connections or openings in the range from 5 microns to 1000 microns.

7. A biomaterial in accordance with Claim 1 wherein the synthetic phosphate is hydroxyapatite or whitlockite.

8. A synthetic biomaterial characterized by a substantially uniform pore volume in the range from 10% to 90% and having a microstructure characterized by a pronounced three dimensional fenestrate structure corresponding to the microstructure of the porous carbonate echinoderm or schleractinian coral skeletal material of marine life and providing a periodic minimal surface, said periodic minimal surface dividing the volume of said material into two interpenetrating regions, each of which is a single, multiply connected domain, said material having a substantially uniform pore size diameter and substantially uniform pore connection or openings in the range from 5 microns to 1000 microns, said synthetic material comprising a base portion of calcium carbonate and a surface layer of calcium phosphate converted from said calcium carbonate.

9. A biomaterial in accordance with Claim 8 wherein the microstructure has the ratio of pore volume to the volume of solid of approximately 1 and has a cross-sectional diameter of both the pore and solid phase of about the same dimension ranging from 5 microns to 1000 microns.

10. A biomaterial in accordance with Claim 8 having pore sizes in the range from 40 to 250 microns.

11. A method for converting a calcium carbonate biomaterial to a phosphate surfaced calcium carbonate biomaterial, the method comprising subjecting said porous biomaterial to hydrothermal chemical exchange with a soluble or solubilized phosphate, said hydrothermal chemical exchange being carried out at a temperature in the range from 200°C to 250°C and at a pressure in the range from $7.0 \cdot 10^3$ kPa to $10.4 \cdot 10^3$ kPa (1000 to 1500 psig) at a phosphate concentration and for a period of time sufficient to convert the surface of said calcium carbonate biomaterial to calcium phosphate.

12. A method in accordance with Claim 11 wherein said phosphate employed in the hydrothermal chemical exchange is $(NH_4)_2 HPO_4$ and wherein $Ca(OH)_2$ is present during the hydrothermal chemical exchange.

13. A method in accordance with Claim 11 wherein said phosphate employed in the hydrothermal chemical exchange is $CaHPO_4{:}2H_2O$ together with $(NH_4)_2 HPO_4$.

14. A method in accordance with Claim 11 wherein the phosphate employed in the hydrothermal chemical exchange for reaction with the carbonate of said porous carbonate skeletal material is phosphate selected from te group consisting of alkali metal phosphates, ammonium orthophosphates, calcium orthophosphates and acid phosphates thereof, orthophosphoric acid and hydrates thereof, and mixtures of weak acdis with phosphates.

15. A method in accordance with Claim 11 wherein said calcium carbonate biomaterial is porous and said soluble or solubilized phosphate is 5% to 30% by weight ammonium phosphate solution, or ammonium dibasic phosphate solution.

16. A method for converting a calcium carbonate biomaterial to a hydroxyapatite surfaced calcium carbonate biomaterial, comprising:

immersing a calcium carbonate sample in a soluble or solubilized phosphate;

heating said calcium carbonate sample in the presence of water or steam at a temperature, pressure and time sufficient to convert the surface of said calcium carbonate biomaterial to said phosphate surfaced biomaterial by hydrothermal exchange of surface carbonate groups for phosphate groups.

17. A method in accordance with Claim 16, wherein said hydrothermal exchange is carried out at a temperature in the range from 100°C to 600°C, a pressure from $10.4 \cdot 10^3$ kPa to $69.0 \cdot 10^3$ kPa (1500 to 10,000 psig) and wherein said soluble or solubilized phosphate is a solution of 5% to 30% by weight ammonium dibasic phosphate.

18. A method for making a biomaterial which comprises:

subjecting a porous calcium carbonate skeletal material to a controlled hydrothermal chemical exchange with a soluble or solubilized phosphate in order to convert a surface layer of said porous calcium carbonate skeletal material to porous phosphate skeletal material; and

filling the pore cavities of said porous material with a polymeric material.

19. A method in accordance with Claim 18 wherein said polymeric material includes an antibiotic and/or a growth factor, preferably a transforming growth factor beta or bone morphogenic factor.

20. A method for preparing a porous calcium carbonate biomaterial having a phosphate surface layer, comprising:

immersing a sample of porous Porites, Alveopora or Goniopora coral in a solution of ammonia dibasic phosphate in order to fill the pore cavities of said coral sample with said ammonium dibasic phosphate solution;

freeze-drying said coral sample;

subjecting said coral sample to hydrothermal chemical exchange at a temperature in the range from 200°C to 250°C, at a pressure in the range from $7.0 \cdot 10^3$ kPa to $10.4 \cdot 10^3$ kPa 1000-1500 psig for a period of time sufficient to convert the surface of said coral sample to phosphate.

Patentansprüche

1. Biomaterial, umfassend einer im wesentlichen aus Calciumcarbonat bestehenden Basisteil mit einer Oberflächenschicht aus einem synthetischen Phosphat.

2. Biomaterial nach Anspruch 1 mit dreidimensionaler porösem Mikrostruktur entsprechend der Mikrostruktur eines porösen Carbonat-Stachelhäuter- oder verhärteten (skleratinischen) Korallen-Skelettmaterials.

3. Biomaterial nach Anspruch 1, wobei die Oberflächenschicht eine Dicke von weniger als etwa 25 µm aufweist.

4. Biomaterial nach Anspruch 2, wobei der Basisteil aus von Korallen herrührendem porösem Calciumcarbonat besteht.

5. Biomaterial nach Anspruch 2, wobei der Basisteil aus der Goniopora- oder Alveolopora-Koralle und die Oberflächenschicht im wesentlichen aus Hydroxyapatit bestehen.

6. Biomaterial nach Anspruch 2 mit einer Porengröße im Bereich von etwa 5 bis 1000 µm und vorzugsweise praktisch gleichförmigen Porenverbindungen oder -öffnungen im Bereich von etwa 5 bis etwa 1000 µm.

7. Biomaterial nach Anspruch 1, wobei das synthetische Phosphat aus Hydroxyapatit oder Whitlockit besteht.

8. Synthetisches Biomaterial, gekennzeichnet durch ein praktisch gleichförmiges Porenvolumen im Bereich von etwa 10% bis etwa 90% und eine Mikrostruktur, die durch eine ausgeprägte dreidimensionale gefensterte Struktur entsprechend der Mikrostruktur des porösen Carbonat-Stachelhäuter- oder gehärteten (skleraktinischen) Korallen-Skelettmaterials von Meereslebewesen gekennzeichnet ist und für eine periodische Minimaloberfläche sorgt, wobei die periodische Minimaloberfläche das Volumen des Materials in zwei einander durchdringende Bereiche unterteilt, von denen jeder aus einer einzelnen, vielschichtig verbundenen Domäne besteht und das Material einen praktisch gleichförmigen Porengrößendurchmesser und praktisch gleichförmige Porenanschlüsse bzw. verbindungen- oder -öffnungen im Bereich von etwa 5 µm bis etwa 1000 µm aufweist und wobei das synthetische Material einen Basisteil aus Calciumcarbonat und eine Oberflächenschicht aus Calciumphosphat umfasst.

9. Biomaterial nach Anspruch 8, wobei die Mikrostruktur ein Verhältnis Porenvolumen/Festsubstanzvolumen von etwa 1 und einen Querschnittsdurchmesser sowohl der Poren- als auch der Festphase von etwa derselben Abmessung im Bereich von etwa 5 µm bis etwa 1000 µm aufweist.

10. Biomaterial nach Anspruch 8 mit Porengrößen im Bereich von etwa 40 bis etwa 250 µm.

11. Verfahren zum Umwandeln eines Calciumcarbonat-Biomaterials in ein Calciumcarbonat-Biomaterial mit Phosphatoberfläche, wobei das poröse Biomaterial einem hydrothermalen chemischen Austausch mit einem löslichen oder löslich gemachten Phosphat unterworfen wird und der hydrothermale chemische Austausch bei einer Temperatur im Bereich von etwa 200°C bis etwa 250°C und einem Druck im Bereich von etwa 1000 bis 1500 psig bei einer solchen Phosphatkonzentration und so lange durchgeführt wird, daß die Oberfläche des Calciumcarbonat-Biomaterials in Calciumphosphat übergeht.

12. Verfahren nach Anspruch 11, wobei das bei dem hydrothermalen chemischen Austausch verwendete Phosphat aus $(NH_4)_2HPO_4$ besteht und während des hydrothermalen chemischen Austauschs $Ca(OH)_2$ vorhanden ist.

13. Verfahren nach Anspruch 11, wobei das bei dem hydrothermalen chemischen Austausch verwendete Phosphat aus $CaHPO_4 \times 2H_2O$ zusammen mit $(NH_4)_2HPO_4$ besteht.

14. Verfahren nach Anspruch 11, wobei das bei dem hydrothermalen chemischen Austausch zur Umsetzung mit dem Carbonat des porösen Carbonat-Skelettmaterials verwendete Phosphat aus einem Phosphat, ausgewählt aus der Gruppe Alkalimetallphosphate, Ammoniumorthophosphate, Calciumorthophosphate und deren saure Phosphate, Orthophosphorsäure und deren Hydrate und Mischung schwacher Säuren mit Phosphaten besteht.

15. Verfahren nach Anspruch 11, wobei das Calciumcarbonat-Biomaterial porös ist und das lösliche oder löslich gemachte Phosphat aus einer etwa 5 bis 30 gewichtsprozentigen Ammoniumphosphatlösung oder zweibasischen Ammoniumphosphatlösung besteht.

16. Verfahren zum Umwandeln eines Calciumcarbonat-Biomaterials in ein Calciumcarbonat-Biomaterial mit Hydroxyapatitoberfläche durch Eintauchen einer Calciumcarbonatprobe in ein lösliches oder löslich gemachtes Phosphat und Erwärmen der Calciumcarbonatprobe in Gegenwart von Wasser oder Dampf auf eine solche Temperatur unter einem solchen Druck und solange, daß die Oberfläche des Calciumcarbonat-Biomaterials durch hydrothermalen Austausch der oberflächlichen Carbonatgruppen gegen Phosphatgruppen in das Biomaterial mit Phosphatoberfläche umgewandelt wird.

17. Verfahren nach Anspruch 16, wobei der hydrothermale Austausch bei einer Temperatur im Bereich von etwa 100°C bis etwa 600°C und einem Druck von etwa 1500 bis etwa 10000 psig durchgeführt wird und wobei das lösliche oder löslich gemachte Phosphat aus einer Lösung von etwa 5 bis etwa 30 Gew.% dibasischen Ammoniumphosphats besteht.

18. Verfahren zur Herstellung eines Biomaterials, bei welchen ein poröses Calciumcarbonat-Skelettmaterial zur Umwandlung einer Oberflächenschicht des porösen Calciumcarbonat-Skelettmaterials in ein poröses Phosphat-Skelettmaterial einem gesteuerten hydrothermalen chemischen Austausch mit einem löslichen oder löslich gemachten Phosphat unterworfen und die Porenhöhlen des porösen Materials mit einem polymeren Material gefüllt werden.

19. Verfahren nach Anspruch 18, wobei das polymere Material ein Antibiotikum und/oder ein Wachstumsfaktor, vorzugsweise einen transformierenden Wachstumsfaktor β oder einen knochenmorphogenen Faktor enthält.

20. Verfahren zur Herstellung eines porösen Calciumcarbonat-Biomaterials mit oberflächlicher Phosphatschicht durch
Eintauchen einer Probe einer porösen Porites-, Alveolopora- oder Goniopora-Koralle in eine Lösung von zweibasischem Ammoniumphosphat zum Füllen der Porenhöhlen der Korallenprobe mit der zweibasischen Ammoniumphosphatlösung,
Gefriertrocknen der Korallenprobe und unter
Unterwerfen der Korallenprobe einem hydrothermalen chemischen Austausch bei einer Temperatur im Bereich von etwa 200°C bis etwa 250°C und einem Druck im Bereich von etwa 1000 bis 1500 psig für eine zur Umwandlung der Oberfläche der Korallenprobe in Phosphat ausreichende Zeit.

Revendications

1. Biomatériau comprenant une partie de base composée de carbonate de calcium contenant essentiellement du matériau de squelette de corail et possédant une couche de surface en phosphate synthétique converti à partir dudit carbonate de calcium, dans laquelle couche de surface la microstructure poreuse dudit matériau de squelette de corail est préservée.

2. Biomatériau selon la revendication 1 possédant une microstructure poreuse tridimensionnelle correspondant à la microstructure d'un matériau de carbonate poreux de squelettes de scléractinies ou d'échinodermes.

3. Biomatériau selon la revendication 1, dans lequel ladite couche superficielle possède une épaisseur inférieure à environ 25 microns.

4. Biomatériau selon la revendication 2, dans lequel ladite partie de base est du carbonate de calcium poreux dérivé de corail.

5. Biomatériau selon la revendication 2, dans lequel ladite partie de base est un corail Gonipora ou Alveolopora et ladite couche de surface se compose essentiellement d'hydroxyapatite.

6. Biomatériau selon la revendication 2 possédant des diamètre des pores de l'ordre de 5 à 1000 microns, et dont les connexions ou ouvertures de pores essentiellement uniformes sont de préférence de l'ordre de 5 microns à 1000 microns.

7. Biomatériau selon la revendication 1, dans lequel le phosphate synthétique est de l'hydroxyapatite ou de la whitlockite.

8. Biomatériau synthétique caractérisé par un volume des pores essentiellement uniforme de l'ordre de 10 à 90 % et possédant une microstructure caractérisée par une structure en fenêtre tridimensionnelle prononcée correspondant à la microstructure d'un matériau marin de carbonate poreux de squelette d'échinodermes ou de scléractinies et

fournissant une surface minimale périodique, ladite surface minimale périodique divisant le volume dudit matériau en deux régions interpénétrantes dont chacune est un seul domaine aux connexions multiples, ledit matériau possédant un diamètre des pores essentiellement uniforme et des connexions ou ouvertures des pores essentiellement uniformes de l'ordre de 5 microns à 1000 microns, ledit matériau synthétique comprenant une partie de base de carbonate de calcium et une couche de surface de phosphate de calcium.

9. Biomatériau selon la revendication 8, dans lequel la microstructure possède un rapport volume des pores/volume solide d'environ 1 et possède un diamètre en coupe transversale d'environ la même dimension, de 5 microns à 1000 microns, tant pour la phase poreuse que pour la phase solide.

10. Biomatériau selon la revendication 8 possédant des diamètres des pores de l'ordre de 40 à 250 microns.

11. Procédé de conversion d'un biomatériau de carbonate de calcium en un biomatériau de carbonate de calcium revêtu de phosphate, le procédé comprenant l'exposition dudit biomatériau poreux à des échanges chimiques hydrothermiques avec du phosphate soluble ou solubilisé, lesdits échanges chimiques hydrothermiques étant effectués à une température de l'ordre de 200°C à 250°C et à une pression de l'ordre de 7,0 . 10^3 kPa à 10.4.10^3 kPa (1000 à 1500 psig) à une concentration de phosphate et pendant une période de temps suffisantes pour convertir la surface dudit biomatériau de carbonate de calcium en phosphate de calcium.

12. Procédé selon la revendication 11 dans lequel ledit phosphate employé dans l'échange chimique hydrothermique est $(NH_4)_2\ HPO_4$ et dans lequel $Ca(OH)_4$ est présent pendant l'échange chimique hydrothermique.

13. Procédé selon la revendication 11, dans lequel ledit phosphate employé dans l'échange chimique hydrothermique est $CaHPO_4{:}2H_2O$ ainsi que $(NH_4)_2\ HPO_4$.

14. Procédé selon la revendication 11 dans lequel le phosphate employé dans l'échange chimique hydrothermique pour la réaction avec le carbonate dudit matériau squelettique de carbonate poreux est un phosphate choisi dans le groupe composé de phosphates alcalins, d'orthophosphates d'ammonium, d'orthophosphates de calcium et de phosphates acides de ceux-ci, d'acide orthophosphorique et d'hydrates de celui-ci et de mélanges d'acides faibles avec des phosphates.

15. Procédé selon la revendication 11, dans lequel ledit biomatériau de carbonate de calcium est poreux et ledit phosphate soluble ou solubilisé représente 5 à 30 % en poids de solution de phosphate d'ammonium ou de solution de phosphate dibasique d'ammonium.

16. Procédé de conversion d'un biomatériau de carbonate de calcium en un biomatériau de carbonate de calcium revêtu d'hydroxyapatite comprenant:
l'immersion d'un échantillon de carbonate de calcium dans un phosphate soluble ou solubilisé;
le chauffage dudit échantillon de carbonate de calcium en présence d'eau ou de vapeur à une température, une pression et pendant une durée suffisantes pour convertir la surface dudit biomatériau de carbonate de calcium en dit biomatériau revêtu de phosphate par échange hydrothermique de radicaux de carbonate de surface par des radicaux phosphate.

17. Procédé selon la revendication 16, dans lequel ledit échange hydrothermique est effectué à une température de l'ordre de 100 à 600°C, à une pression de 10.4.10^3 kPa à 69,0. 10^3 kPa (1500 à 10000 psig) et dans lequel ledit phosphate soluble ou solubilisé est une solution de 5 à 30 % environ en poids de phosphate dibasique d'ammonium.

18. Procédé de fabrication d'un biomatériau qui comprend: l'exposition d'un matériau squelettique de carbonate de calcium poreux à un échange chimique hydrothermique contrôlé avec un phosphate soluble ou solubilisé afin de convertir une couche de surface dudit matériau squelettique de carbonate de calcium poreux en un matériau squelettique de phosphate poreux et
le remplissage des cavités poreuses dudit matériau poreux avec un matériau polymère.

19. Procédé selon la revendication 18 dans lequel ledit matériau polymère comprend un antibiotique et/ou un facteur de croissance, de préférence un facteur bêta de croissance de transformation ou un facteur morphogène osseux.

20. Procédé de préparation d'un biomatériau de carbonate de calcium poreux possédant une couche de surface de phosphate comprenant:
l'immersion d'un Oéchantillon de corail poreux Porites, Alvelopora ou Gonipora dans une solution de phosphate

dibasique d'ammonium afin de remplir les cavités poreuses dudit échantillon de corail avec ladite solution de phosphate dibasique d'ammonium;
la lyophilisation dudit échantillon de corail;
l'exposition dudit échantillon de corail à des échanges chimiques hydrothermiques à une température de l'ordre de 200°C à 250°C et à une pression de l'ordre de $7,0 \times 10^3$ kPa à $10.4.10^3$ kPa (1000 - 1500 psig) pendant une période de temps suffisante pour convertir la surface dudit échantillon de corail en phosphate.

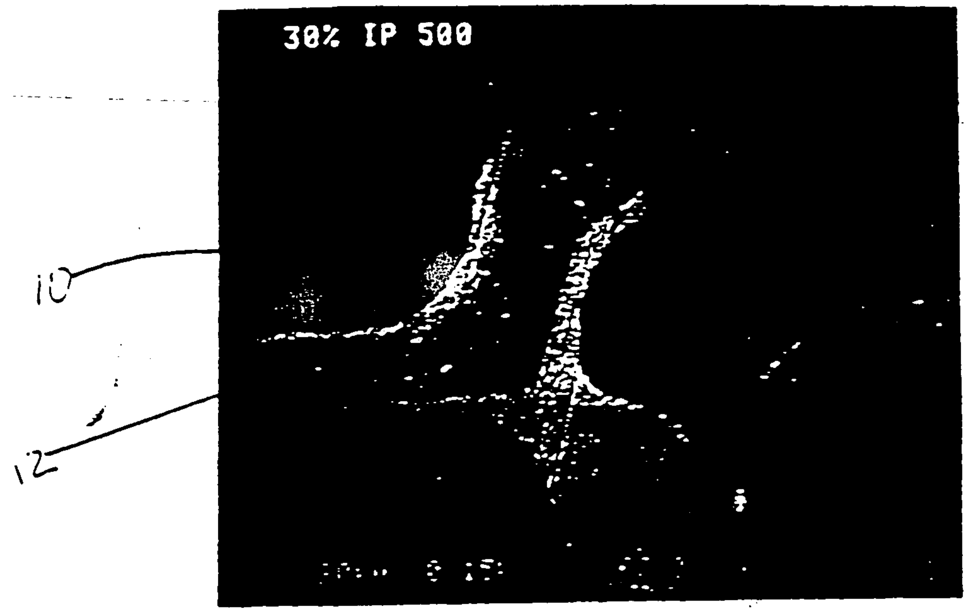

FIG. 1

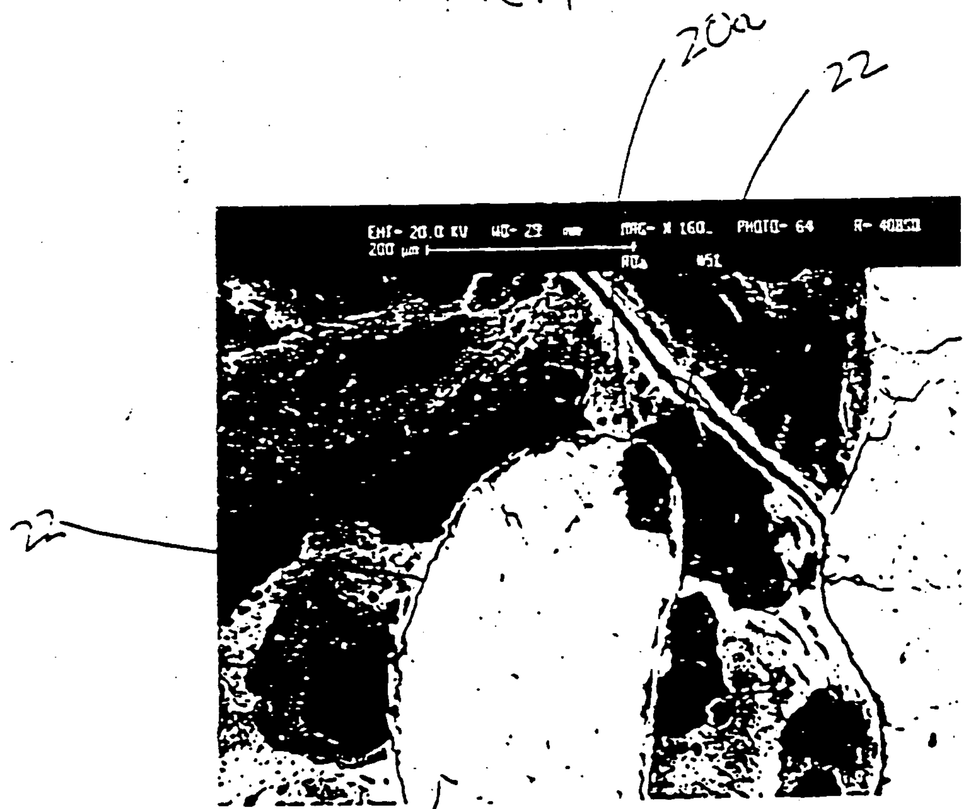

FIG. 2